REMARKS

Applicant respectfully requests reconsideration. Claims 42-53 and 56-78 were previously pending in this application. Claims 42 and 71 are amended herein to add the limitations of prior pending claims 56 and 74. Claims 56-58, 70 and 74 are canceled. New claims 79-80 are added to add the limitation that an antigen is administered to the subject. As a result, claims 42-53, 59-69, 71-73, and 75-78 are still pending for examination with claims 42 and 71 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 42-53 and 56-78 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The Examiner has maintained the rejection and dismissed Applicants arguments because the Examiner contends that the art of record establishes the unpredictability of a method of treating cancer by administering a CpG oligonucleotide. Applicant's disagree.

Although some of the post-filing art suggests unpredictability the post-filing art as a whole supports the effectiveness of CpG oligonucleotides in the treatment of cancer. When the issue of predictability is viewed in the context of the other Wands factors that are useful in determining undue experimentation, one of skill in the art would conclude that the practice of the invention would not have required undue experimentation at the time the application was filed.

A claimed invention is enabled if it can be practiced (i.e., made and used) without undue experimentation. Whether the experimentation is undue is determined by an analysis of the Wands factors. These factors include the nature of the invention, the breadth of the claims, the state of the art, the level of ordinary skill in the art, the level of predictability in the art, the amount of guidance provided by the specification, the existence of working examples, and the amount of experimentation required. The factors must be considered in their totality with no one factor being dispositive. Whether undue experimentation would be required is determined at the time the application was filed. An analysis of these factors as they relate to the claimed methods is provided below.

Nature of the Invention. The invention relates to the discovery that immunostimulatory CpG oligonucleotides produce a systemic immune response in a subject that is useful in the treatment of cancer. It had been known that certain types of infections and bacterial extracts trigger immune responses that can cause regressions of cancer. The present invention is based at least in part on the discovery that the immune stimulatory effects of bacterial DNA result from the presence of unmethylated CpG motifs, which are methylated and suppressed in vertebrate DNA, which is not immune stimulatory. The immune system has thus evolved a defense mechanism against infection that is based on immune recognition of CpG motifs, which trigger a protective immune response. One aspect of the invention is the recognition that the same type of immune response that is triggered through this defense pathway can be redirected against cancer, using synthetic oligonucleotides that mimic bacterial DNA. From this discovery of the mechanism of immune activation by bacterial DNA, the invention provides for the use of synthetic oligonucleotides containing these CpG motifs to induce a pattern of immune activation, which is capable of causing tumor regression. Clinical trials involving administration of bacterial DNA to humans demonstrated positive effects in cancer patients. (See e.g., Tokunaga et al Jpn. J. Infect. Dis 52, 1-11, 1999.)

Breadth of the Claims. The claims relate to methods for treating cancer by administering a CpG oligonucleotide to a subject. The subject is administered an immunostimulatory unmethylated CpG oligonucleotide either alone or in combination with a chemotherapeutic agent (claim 43 and 72), an immunotherapeutic agent (claim 44 and 73) or an antigen (claims 79-80). The oligonucleotide is 8-100 nucleotides in length and has at least one phosphorothioate backbone modification.

Amount of Direction or Guidance Provided by Specification. The specification provides a description of the genus of immunostimulatory CpG oligonucleotides. (See pages 15-17 and 21-24). The specification also provides representative species of these oligonucleotides, as well as data demonstrating their immunostimulatory activity. (See for example Table 1 and the Examples). The specification teaches how to make and how to formulate the oligonucleotides. In particular, the specification teaches that the oligonucleotides can have varying lengths and sequences but the critical element is the unmethylated CG dinucleotide. (See pages 15-17 and 21-24).

The claimed CpG oligonucleotides all have the common structural property that they include an unmethylated CpG dinucleotide. The use of this class of oligonucleotides for the treatment of cancer is first described by Application. Since the priority date of the instant patent application numerous groups have begun working on these oligonucleotides and they have since been described in many patents and patent applications. It is the unmethylated CpG dinucleotide that confers the immune stimulating properties on the oligonucleotide. It is now believed that CpG oligonucleotides act through a common cellular receptor, TLR9. It is believed that CpG oligonucleotides are recognized by TLR9 and that this leads to the promotion of an immune response in which a Th1 response is favored and in which B cells and NK cells are activated. It is this common mechanism that unifies the resultant immune response produced by CpG oligonucleotides.

The specification provides guidance for the type of phosphate backbone modifications that can be incorporated in the CpG oligonucleotides of the invention. Applicants have provided sufficient reasons for why one of skill in the art would expect the claimed class of CpG oligonucleotides to function in the manner set forth in the claims. Although Applicant believes that it is unnecessary for enablement, Applicant has amended the claim to add the limitation that the backbone modification is a phosphorothioate modification. Many of the immune stimulatory CpG oligonucleotides tested and described in the patent application have a phosphorothioate modification.

The direction provided by the specification is adequate to describe the composition and length of CpG oligonucleotide sequences. As described in greater detail below, the specification provides description and data that is consistent with the claimed invention as well as the discoveries that have taken place since the invention.

In the specification Applicants have demonstrated that oligonucleotides containing an unmethylated CpG are effective at stimulating B-cell proliferation (Table 1), IgM secretion (page 26), IL-6 production (pages 26-27, Table 3, pages 28-30, and Table 4), induction of IL-12 (pages 30-32 and Tables 5-6), induction of IFN-γ (pages 30-32 and Tables 5-6), and induction of NK Cell Stimulatory Activity (pages 36-44 and Tables 8-11). The description and the data found in the specification establish a pattern of immune stimulation which is consistent with the treatment of

cancer. The data is sufficient to establish to one of skill in the art that this class of drugs is sufficient to promote an immune response which helps the host body's immune system attack the cancer.

Working Examples.

The Examiner has stated that the specification has no working examples indicating that CpG oligonucleotides can be useful for treating any kind of cancer. The Examiner states that the data presented in the specification is not sufficient to establish that the claimed oligonucleotides will be useful for the treatment of cancer. The Examiner invites the Applicants to identify places in the specification providing a correlation between the scope of the claims in the specification. The Examiner further cites Zips et al. (New Anti-cancer Agents: In Vitro and In Vivo Evaluation, 2005, In vivo, 19:1-7) for the teaching that in vitro data is not sufficient to establish tumor response to drugs.

In the specification, Applicants have taught that oligonucleotides containing an unmethylated CpG dinucleotide produced an immune response that is consistent with the treatment of cancer. Applicants have taught routes of administration. Applicants have provided numerous examples of oligonucleotides falling within the genus of molecules. Significant amounts of data demonstrating the specific effects of CpG oligonucleotides are provided in the specification. The data confirms the specificity of the claimed motif by showing oligonucleotides having an unmethylated CpG dinucleotide are capable of inducing an immune response whereas oligonucleotides having the same sequence of nucleotides but a methylated C instead of an unmethylated C lose activity.

Zips et al does not relate to CpG oligonucleotides. One distinction between Applicants invention and other systems for testing drugs for the treatment of cancer is that the CpG oligonucleotides of the invention are acting through stimulation of an immune response in a host. That immune response in the host then attacks the cancer and produces the therapeutic result. Many other anti-cancer drugs have affects on localized systems such as the cancer cells themselves or the vasculature associated with the tumor. These types of drugs require targeting and therapeutic

activity at localized regions. Unlike these drugs, CpG oligonucleotides when exposed to immune cells enhance the body's reaction to the tumor.

At the time the patent application was filed it was known in the art that induction of interferon-γ (IFN-γ), IL-12, and IL-6 as well as NK cell activation was useful in the treatment of cancer. The following summaries of references published prior to or around the priority date of the instant application describe the state of the art with respect to immune system activation and the treatment of cancer. Copies are enclosed with the attached IDS.

Trinchieri et al., Blood, V.84, December 15, 1994, p. 4008 is a review article describing IL-12 in the production of cytotoxic lymphocytes. Page 4021 describes the role of IL-12 in anti-tumor immunity. Specifically, it is taught that "studies using transplantable tumors in experimental animals have shown a dramatic affect of IL-12 in decreasing tumor growth and metastasis formation and in significantly delaying death.[134] Systemic Daily Treatment (5 days per week) had a significant inhibitory affect on the growth of metastasis induced by intravenous injection of B16 melanoma cells and efficiently inhibited the growth of subcutaneously injected tumors, even when treatment was initiated two weeks after tumor inoculation.[123] An inhibitory affect of IL-12 on tumor growth, with a greater than two-fold increase in survival of inoculated animals, was also observed with the reticulum cell sarcoma M5076 and with the renal cell adenocarcinoma renca.[134] In this latter tumor, complete remission, especially with peritumoral injection of IL-12, was observed in some animals; reinjection of the renca cells in the "cured" animals resulted in delayed growth of the tumor, suggesting that IL-12 may induce a memory immune response against the tumor.[134]" (Paragraph spanning 4021-4022).

Brunda et al. Journal Leukocyte Biology, V.55, February 1994 is a review article describing IL-12. Pages 285-286 of Brunda et al. describe the use of IL-12 in vivo in numerous murine tumor models. It is taught that "a large body of experimental evidence has now been accumulated demonstrating that IL-12 has potent antimetastatic and antitumor activity in a number of murine tumor models. The therapeutic activity of IL-12 has been observed in four of four murine metastasis models, including both pulmonary and hepatic metastases." (P. 285, first column, last paragraph).

U.S. Patent No. 4,883,662 issued on November 28, 1989, describes an in vivo method for increasing NK cells in the blood of cancer patients because such NK cells have known activity against tumor cells. (Abstract). In the summary of the invention it is taught that "it has been established that increasing such natural killer cells is an important component of the immune system, and that accordingly the present method should be a decided advantage in cancer treatment. ...furthermore, it is believed at least two-fold increase in natural killer cells should be affected in order to obtain meaningful treatment results."

Hayashi et al., Proceeding of the Japan Academy, Series B: Physical and Biological Sciences, 1994, 70, 205, describes immunotherapy for the treatment of cancer. The abstract teaches that immunotherapy with BCG-CWS results in IFN-γ induction. It is further taught that cancer patients experiencing IFN-γ induction and/or strong skin reaction survived for longer periods of time than those patients showing no IFN-γ induction, who died after a short period.

The above described papers were published prior to or around the priority date of the instant application. The papers establish that one of skill in the art would have recognized the utility of a drug which is effective in inducing IL-12, IFN-γ and NK cell activation as a compound which would be useful in the treatment of cancer. Thus, at the time of the invention the data presented in the specification would have been sufficient to demonstrate to one of skill in the art that unmethylated CpG oligonucleotides are useful in the treatment of cancer. On page 4 of the Office Action the Examiner states "although the specification established a pattern of immune stimulation by this class of oligonucleotides and such induction of cytokines may be involved in the cancer regression; the correlation between the induction of the three disclosed cytokines and treatment of cancer has not been clearly established." The Examiner does not provide any evidence to support this statement. Regardless, Applicant has presented sufficient evidence to establish the correlation between the induction of the disclosed cytokines as well as NK cell activation and the treatment of cancer.

Unpredictably of the Art and State of the Prior Art

The Examiner has relied on teachings derived solely from post-filing references to establish the unpredictability of the invention. It is appropriate to use post-filing references to establish

whether an invention was unpredictable at the time the patent application was filed. The teachings of these post-fling references must be considered in their entirety. To the extent that the references include inconsistent statements, the teachings contained therein must be balanced carefully to reach a conclusion on the predictability or unpredictability of a claimed invention at the time the application was filed. Each of the references cited by the Examiner contain some statements relating to general issues faced by drugs in development. However when each of the references is considered in their entirety it is clear that the references support feasibility of the claimed invention, particularly when the references are specifically addressing the use of CpG oligonucleotides in therapy. Balancing the teachings of this group of references as a whole, one of skill in the art would be led to the conclusion that at the time of the invention, the use of the claimed invention could be achieved without undue experimentation particularly when considered in the context of the specification and the knowledge of the skilled artisan at the time of the invention.

In response to the prior Office Action, Applicants presented several arguments rebutting the Examiner's rejection stating that Agrawal et al. establishes the unpredictability of the invention. In the current Office Action the Examiner has addressed only a sub-set of Applicants' arguments. Applicants will address first the Examiner's comments in the most recent Office Action and then will reiterate all of the arguments previously presented but not addressed by the Examiner.

On page 3 of the Office Action the Examiner states that "although Agrawal teaches the presence of unmethylated CpG dinucleotides are essential for the induction of immunostimulatory activity, the induction of cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species." The section of Agrawal on page 116 referred to by the Examiner actually states the following, "the recognition of CpG DNA by innate immune system cells, macrophages and DCs results in: (1) the secretion of cytokines, such as IL-12, IL-6, tumor necrosis factor α (TNF-α) and IFN-γ...the CpG DNA also induces IFN-α and IFN-β, which induce NK-cell lytic activity [4, 26]. *The secreted cytokines are known to provide non-specific protection against infections and cancers* [27]. Several CpG DNA candidates are under pre-clinical and clinical evaluation against a broad range of infectious diseases and cancers (Table 1). However, the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of

administration and the host animal species [11]." (emphasis added) The cited paragraph confirms that CpG DNA oligonucleotides are currently in clinical evaluation for cancers. If the unpredictability of the claimed invention was so great at the time that Agrawal wrote the paper in March of 2002, the FDA would not have allowed the clinical evaluation of the drug in human patients.

In the sentence spanning pages 3-4 of the Office Action the Examiner points to an argument presented by Applicants in response to the prior Office Action related to dosages and concludes that "such statement does enable a skilled artisan to design the dose of administration of CpG molecules in the treatment of cancer." Initially, it is unclear whether the Examiner intended to state that the statement does not enable a skilled artisan. If so, the Examiner has misunderstood Applicants arguments. Applicant did not assert that such a statement enables a skilled artisan to design the dose of administration of CpG molecules in the treatment of cancer. Rather, Applicant presented the following argument in response to the Examiner's assertion that Agrawal et al. teaches the dose and route of administration of CpG oligonucleotides is not yet known.

The Examiner had pointed to the teaching in Agrawal et al. that the pattern of cytokines in vivo depends on the sequences flanking the CpG dinucleotide "as well as the dose and the route of administration which are not yet known." (Page 8-9 of prior office action). Although Agrawal teaches the first part of the quoted sentence, Applicants could not identify where Agrawal states that the dose and route of administration are not yet known. Agrawal describes preliminary data from early stage clinical trials in the treatment of cancer (lymphoma, melanoma and basal cell carcinoma). If the compound is being administered to human patients in a clinical trial, at least preliminary therapeutically acceptable doses and routes of administration have been identified. Additionally, the last sentence of the quoted paragraph explicitly states and approximate dose, i.e., that "CpG DNA elicit affects at $\mu g\ kg^{-1}$ doses." (Page 116, 2nd column, last sentence). Applicant did not assert that such a recitation of dose enabled the claims. but rather addressed the specific point made by the Examiner.

On page 4 of the Office Action, the Examiner states that "Agrawal, (published in 2002) well after the filing date of the instant application, teach that that the medicinal chemistry of CpG DNA have just begun and need further fine-tuning, which clearly indicates that at the time of filing of the

instant application the Applicants were not enabled for the claimed invention, which is a method of treating various cancers comprising administering CpG immunostimulatory oligonucleotides." The Examiner does not appear to be applying the appropriate legal standard to the analysis. The fact that medicinal chemistry of CpG DNA needs further fine-tuning does not "clearly indicate" that the invention was not enabled. "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re: Angstadt 537 F.2D 498, 504, 190 USPQ 124, 129, (CCPA 1976)" "The fact the experimentation may be complex does not necessarily make it undue. If the art typically engages in such experimentation. In re: Certain limited-charge cell culture microcarriers, 221 USPQ 1165, 1174) Int'l Trade Comm'n 1983)." (MPEP Section 2164.01). The use of any drug in human patients requires further fine-tuning. Even commercially available FDA approved drugs are subject to further research and development. Experiments involving fine-tuning to understand the medicinal chemistry potential are not undue experimentation.

The Examiner on page 4 of the Office Action has reiterated that Peterson et al., Schuh et al., Bibby et al. and Siajo et al., support the unpredictability of the treatment of cancer because each reference teaches that numerous agents which show promise in pre-clinical models have minimal clinical activity. Applicants reiterate that none of the cited references describe the use of CpG oligonucleotides. If such references establish the unpredictability of the treatment of cancer for drugs unrelated to those described with the references themselves then, the Patent Office could never issue a claim directed to the method of treatment of cancer in the absence of clinical data. There is no nexus between the drugs described in each of these references and CpG oligonucleotides. If broad unpredictability can be concluded from these references then such unpredictability of any pre-clinical data should be applied to any drug for the treatment of cancer.

On page 5 of the Office Action it is stated that "thus, since the prior art cited clearly communicates the unpredictability in the treatment of cancers and since the specification does not provide a skilled artisan the guidance to practice such; the claimed invention requires an undue experimentation." Applicants clarify for the record that all of the art cited by the Examiner with respect to the lack of enablement rejection are post-filing references. None of the art is "prior art."

The post-filing references can only be cited to establish what was known in the art at the time the patent application was filed.

The following articles describe clinical trials which are on-going or have been performed using CpG oligonucleotides. Although in one phase III trial sufficient responses over base line chemotherapy were not observed in quantities that would justify continuance of the trial, numerous other trials have demonstrated positive and encouraging results. For instance, a phase III trial involving the use of CpG oligonucleotide in combination with a cancer vaccine was recently initiated as a result of positive phase II data.

Danila Valmori, Naira E. Souleimanian, Valeria Tosello, Nina Bhardwaj, Sylvia Adams, David O'Neill, Anna Pavlick, Juliet B. Escalon, Crystal M. Cruz, Angelica Angiulli, Francesca Angiulli, Gregory Mears, Susan M. Vogel, Linda Pan, Achim A. Jungbluth, Eric W. Hoffmann, Ralph Venhaus, Gerd Ritter, Lloyd J. Old, and Maha Ayyoub. Vaccination with NY-ESO-1 protein and CpG in Montanide induces integrated antibody/Th1 responses and CD8 T cells through cross-priming. PNAS. Vol. 104, no. 21: 8947-8952.

Barbara G. Molenkamp, Paul A. M. van Leeuwen, Sybren Meijer, Berbe J. R. Sluijter, Pepijn G.J.T.B. Wijnands, Arnold Baars, Alfons J. M. van den Eertwegh, Rik J. Scheper, and Tanja D. de Gruijl. Intradermal CpG-B Activates Both Plasmacytoid and Myeloid Dendritic Cells in the Sentinel Lymph Node of Melanoma Patients. Clin Cancer Res 2007;13(10).

Appay, V., C. Jandus, V. Voelter, S. Reynard, S. E. Coupland, D. Rimoldi, D. Lienard, P. Guillaume, A. M. Krieg, J. C. Cerottini, P. Romero, S. Leyvraz, N. Rufer, and D. E. Speiser. 2006. New generation vaccine induces effective melanoma-specific CD8+ T cells in the circulation but not in the tumor site. J Immunol. 177:1670-1678.

Link, B., Z. Ballas, D. Weisdorf, J. E. Wooldridge, M. Shannon, W. Rasmussen, A. Krieg, and G. Weiner. 2006. Oligodeoxynucleotide CPG 7909 Delivered as Intravenous Infusion Demonstrates Immunologic Modulation in Patients with Previously Treated Non-Hodgkin's Lymphoma. J Immunother. 29:558-568.

Cooper, C. L., H. L. Davis, J. B. Angel, M. L. Morris, S. M. Elfer, I. Seguin, A. M. Krieg, and D. W. Cameron. 2005. CPG 7909 adjuvant improves hepatitis B virus vaccine seroprotection in antiretroviral-treated HIV-infected adults. AIDS 19:1473-1479.

Speiser, D. E., D. Lienard, N. Rufer, V. Rubio-Godoy, D. Rimoldi, F. Lejeune, A. M. Krieg, J. C. Cerottini, and P. Romero. 2005. Rapid and strong human CD8(+) T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909. J Clin.Invest 115:739-746.

Krieg, A. M., S. M. Efler, M. Wittpoth, M. J. Al Adhami, and H. L. Davis. 2004. Induction of systemic TH1-like innate immunity in normal volunteers following subcutaneous but not intravenous administration of CPG 7909, a synthetic B-class CpG oligodeoxynucleotide TLR9 agonist. J Immunother. 27:460-471.

Cooper, C. L., H. Davis, M. L. Morris, S. M. Efler, A. Krieg, Y. Li, C. Laframboise, M. J. Al Adhami, Y. Khaliq, I. Sequin, and D. W. Cameron. 2004. Safety and Immunogenicity of CpG 7909 Injection as an Adjuvant to Fluarix Influenza Vaccine. Vaccine 22:3136-3143.

Cooper, C. L., H. Davis, M. L. Morris, S. M. Efler, M. J. Al Adhami, A. Krieg, D. W. Cameron, and J. Heathcoat. 2004. CpG 7909, an immunostimulatory TLR9 agonist oligodeoxynucleotide, as adjuvant to Engerix-B HBV vaccine in healthy adults: A double-blind Phase I/II study. J Clin.Immunol 24:693-702.

Siegrist, C. A., M. Pihlgren, C. Tougne, S. M. Efler, M. L. Morris, M. J. Aladhami, D. W. Cameron, C. L. Cooper, J. Heathcote, H. L. Davis, and P. H. Lambert. 2004. Co-administration of CpG oligonucleotides enhances the late affinity maturation process of human anti-hepatitis B vaccine response. Vaccine 23:615-622.

Press Release, June 2007, "Coley Pharmaceutical Group Announces Pfizer's Discontinuation of Clinical Trials for PF-3512676 Combined with Cytotoxic Chemotherapy in Advanced Non Small Cell Lung Cancer"

On balance the teachings of the prior art as well as the post-filing art overall are consistent with and support the use of CpG oligonucleotides in the treatment of cancer based on the data and descriptions in the patent application as filed. Miscellaneous statements in references referring to future work, fine-tuning, optimization or additional experimentation to prove clinical efficacy do not support a finding of unpredictability of the claimed invention.

Further, Agrawal is a review article summarizing numerous studies performed on CpG oligonucleotides and their effects on immune stimulation and potential use as therapeutics. Agrawal has described the therapeutic potential and utility of CpG DNA in human systems, including the use for treating cancer. A significant amount of discussion in Agrawal is directed to the production of second-generation immunostimulatory DNA that do not include CpG motifs. Although Agrawal recognizes that production of specific cytokines can be optimized by using specific CpG motifs with flanking sequences as well as dose and route of administration, Agrawal does not suggest that CpG DNA is not useful therapeutically. The sections highlighted by the Examiner simply refer to optimization of the molecules. Demonstration that molecules can be optimized is not evidence that the invention as a whole is unpredictable. On page 116 Agrawal describes CpG in clinical trials and states that "Significant progress has been made in understanding the immunological and pharmacological affects of the first-generation CpG DNA molecules." (Second column, third paragraph.) Agrawal concludes by stating that "it is evident that CpG DNA is a powerful tool to

modulate the immune system and can be exploited to treat a wide variety of diseases quite economically. Studies on the medicinal chemistry of CpG DNA have just begun and the preliminary results indicate several possible ways of further fine-tuning the immunomodulatory affects of first-generation CpG DNA by introducing site-specific chemical modifications." (Page 199, 2nd column 2nd paragraph).

In the prior Office Action the Examiner had addressed Applicants' prior arguments with respect to Agrawal. According to the Examiner Agrawal et al. suggests undue experimentation would be needed for treatment methods using CpG containing oligonucleotides because although Agrawal describes significant progress, "only limited data are available on optimized CpG DNA agents in human clinical trials." The fact that limited data is available on optimized CpG DNA agents does not support the unpredictability of the invention or demonstrate that the invention would require undue experimentation. The claimed invention does not require the use of "optimized CpG DNA agents." Additionally, the fact that only limited data is available in human clinical trials does not suggest the invention would not work.

At the time of the filing of the patent application, Applicants described a class of molecules useful for the treatment of cancer. Applicants fundamental invention is based at least in part on the discovery that the immune system detects bacterial DNA by the presence of unmethylated nucleotides, which can be present in a wide variety of base contexts. The applicant was the first to recognize that these immune activating effects of bacterial DNA could be reproduced using synthetic oligonucleotides containing unmethylated CpG. The fact that an author suggests that the medicinal chemistry of this class of molecules needs further fine-tuning at a later date does not indicate that the claimed invention lacks enablement. Even after drugs are used successfully in humans, researchers continue to do research and fine-tune various aspects of the drug. Optimization or preferential selection of species at a later point in time does not render the use of a genus of compounds unpredictable at an earlier time point.

In totality it appears that the only data acceptable to the patent office for establishing enablement is evidence of clinical success. However, the law is well established that a clinical trial is not required for enablement. It is not proper for the Examiner to require clinical data to support the enablement of the invention. Although other therapeutic agents which had shown activity in

pre-clinical models may have had minimal clinical activity as described in these references, this is not true with CpG oligonucleotides. As shown in the specification, Applicants generated pre-clinical data on CpG oligonucleotides that demonstrated activity consistent with the treatment of cancer. Currently there are a number of clinical trials being conducted with CpG oligonucleotides, including trials for the treatment of cancer with CpG oligonucleotides.

Krieg et al. (Nat. Revs. 2006 v. 5 p. 471 (discussed in response to the last office action) overall teaches the therapeutic value of CpG oligonucleotides in the treatment of diseases such as cancer. Applicant pointed out that Krieg et al describe "encouraging evidence for the capacity of TLR9 activation to induce a TH1-like cytokine response in human cancer patients has been reported recently in studies in dendritic cells isolated from primary human tumours[100] and in lymphoma patients treated with a CpG ODN alone or together with an antitumour antibody." (Page 477, second column, last paragraph). In Table 2 on page 478 of Krieg, the human clinical trials being conducted or completed as of 1996 are listed. The clinical trials for cancer include a phase I monotherapy, a phase II vaccine therapy, and a phase I, II and III combination therapy. Additionally, a 2007 review article, Krieg, J. Clin Invest. 117, p. 1184, 2007 (attached as Exhibit 2), describes a summary of TLR9 agonists in cancer therapy. Table 2 lists published oncology clinical trials with TLR9 agonists and Table 3 lists ongoing oncology clinical trials with TLR9 agonists. Thus, the fact that several references teach that completely unrelated drugs showing preclinical activity but minimal clinical activity is not relevant to the predictability of CpG oligonucleotides which are already demonstrating promise in clinical trials.

The Examiner has pointed to a statement in Krieg stating that it demonstrated the unpredictability of the invention. However, literature articles always include cautions on therapeutic benefits of drugs. When read in its entirety the reference is supportive of the claimed invention.

It is noted that the data need not support that every CpG oligonucleotide/antigen /route of administration/dosage combination through every route of administration work equivalently or even work at all in order to meet the enablement requirement. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 1984 (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of

candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide/antigen/route of administration/dosage combination would not work equivalently or that it is possible that some rare combinations might not work at all is not a sufficient basis for rejecting the claims.

Quantity of Experimentation

The Examiner had also addressed the quantity of experimentation. According to the Examiner, "The amount of additional experimentation is deemed to be undue because in order to practice the claimed invention with a reasonable expectation of success, one of skill in the art would have to show evidence overcoming art recognized problems that the broadly claimed CpG-containing oligonucleotides would not work for treating or preventing any cancer." (Prior Office Action). Applicants disagree. Applicants have taught in the specification that a class of compounds is useful for treating cancer. Exemplary dosages and routes of administration are provided. The class of compounds includes oligonucleotides having a CpG motif. Methods are known in the art for synthesizing oligonucleotides containing a CpG motif. The oligonucleotides can be purchased from numerous commercial sources. The oligonucleotide once synthesized could be administered to a subject having cancer, as is currently being performed in on-going human clinical trials. It is unclear to Applicants why the experimentation required to perform the method would be considered to be undue. One of skill in the art would simply need to follow the guidance provided in the specification using a class of molecules which is commercially available or easily synthesized.

Accordingly, withdrawal of the rejection of claims 42-53, 59-69, 71-73, and 75-78 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: October 30, 2007

Respectfully submitted,

By _____

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